Understanding the Approval Process for New Cancer Drugs

Information from the National Cancer Institute about cancer research studies

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Preface

Since June 1996, forty five new cancer-related drugs , or new uses for drugs already on the market have been approved by the Food and Drug Administration, the division of the Department of Health and Human Services charged with ensuring the safety and effectiveness of new drugs before they can go on the market.(http://www.fda.gov/oashi/cancer/cdrug.html) Some of these drugs treat cancer, some alleviate pain and other symptoms, and, in one case, reduce the risk of invasive cancer in people who are considered high-risk. The FDA relied on the results of clinical trials in making every one of these approvals. Without reliable information about a drug's effects on humans, it would be impossible to approve any drug for widespread use.

When considering a new drug, the FDA faces two challenges: first, making sure that the drug is safe and effective before it is made widely available; and second, ensuring that drugs which show promise are made available as quickly as possible to the people they can help. To deal with these challenges, the FDA maintains a rigorous review process but also has measures in place to make some drugs available in special cases. This material derived from the cancerTrials web site is designed to acquaint you with the drug approval process and point you to other resources for learning more about it.

Note on Web navigation:

Click on the red text to navigate to a highlighted web site. You must have the Adobe Acrobat WebLink plug-in installed for this feature to work properly.

An Introduction to the FDA's Role

One Example: Herceptin for Breast Cancer

Before September 25, 1998, women with advanced breast cancer who wanted to take the drug Herceptin needed to enroll in a clinical trial. But after that date, they could obtain it through their physicians, like any other prescription drug. That's because Herceptin had received official approval from the Food and Drug Administration (FDA). In the months leading up to approval, researchers had reported promising results from studies of women with advanced breast cancer whose tumor cells have extra copies of a protein called HER2. Herceptin is designed to target that protein and kill the cancer cells, leaving healthy cells alone. One group of researchers found that women who took the drug along with standard chemotherapy survived longer than those who only had chemotherapy. Another group found that Herceptin alone could help some women whose cancer was not responding to chemotherapy. A few months later, after carefully reviewing the results and weighing the benefits against the risks of side effects, the FDA approved the drug for use in women with HER2-positive, advanced breast cancer.

Approval is only one step in the drug development process. In fact, the FDA estimates that, on average, it takes eight and a half years to study and test a new drug before it can be approved for the general public. That includes early laboratory and animal testing, as well as the clinical trials that evaluate the drugs in humans. The FDA plays a key role at three main points in this process:

- determining whether or not a new drug shows enough promise to be given to people in clinical trials
- once clinical trials begin, deciding whether or not they should continue, based on reports of efficacy and adverse reactions
- when clinical trials are completed, deciding whether or not the drug can be sold to the public and what its label should say about directions for use, side effects, warnings, and the like.

To make these decisions, the FDA must review studies submitted by the drug's sponsor (usually the manufacturer), evaluate any adverse reports from preclinical studies and clinical trials (that is, reports of side effects or complications), and review the adequacy of the chemistry and manufacturing. This process is lengthy, but it is meant to ensure that only beneficial drugs with acceptable side effects will make their way into the hands of the public. At the same time, recent legislative mandates and streamlined procedures within the FDA accelerated the

approval of effective drugs, especially for serious illnesses such as cancer. In addition, specific provisions make some drugs available to patients with special needs even before the approval process is complete.

FDA Regulations and U.S. Drug Law: A Short History

The present system of FDA regulation has evolved over the course of this century. Before 1906, there were no laws guaranteeing the quality of medicines and no regulations requiring a doctor's prescription for medications.

So-called "patent" medicines, many containing dangerous ingredients, were advertised with outlandish health claims and widely marketed in the United States. By the turn of the century, it was apparent that some form of regulation was necessary. The following major developments in U.S. drug laws and FDA regulations demonstrate how the federal power to regulate drugs, which began as a simple effort to identify fraudulent medicine, has evolved into a complex system dedicated to ensuring the health and safety of the public. They also suggest how the government has tried to balance public safety with the desire to widen access to promising drugs for life-threatening illnesses.

Food and Drugs Act (1906): This law targeted false and fraudulent "patent" medicines and required that drugs meet standards of strength and purity. A few years later, this act was extended to cover not only a ban on false or misleading labeling pertaining to ingredients, but also to claims of effectiveness. The 1906 act lacked "teeth"—it was difficult to enforce and was very narrowly applied.

Federal Food, Drug, and Cosmetic Act (1938): It was not until 1937, when 107 people died from a poison in the patent medicine marketed as "Elixir Sulfanilamide," that Congress passed a more stringent drug law. The FDC Act required manufacturers to prove the safety of drugs, authorized factory inspections, and established penalties for fraudulent claims and misleading labels.

Durham-Humphrey Amendment (1951): This was the first federal law requiring a physician's prescription for drugs "unsafe for self-medication."

Kefauver-Harris Drug Amendments (1962): In Western Europe, thousands of babies were born with birth defects because their mothers had taken the sedative Thalidomide during pregnancy. A delayed review process prevented the drug from being marketed in the U.S., where it was being studied in a large number of subjects. In response to this tragedy, the Kefauver-Harris amendment mandated that manufacturers prove their drugs were effective for specific medical purposes, as well as safe, through "adequate and well-controlled" studies. This law applied retroactively to all drugs introduced since the 1938 FDC Act. Firms were also required to report all adverse reactions to the FDA and to include complete information (about adverse effects as well as benefits) for physicians in advertisements. For the first time, informed consent (http://cancertrials.nci.nih.gov/NCI_CANCER_TRIALS/zones/TrialInfo/Deciding/InformedConsent) was required from patients participating in studies of a new drug.

Orphan Drug Act (1983): Orphan drugs are intended to treat rare diseases and conditions for which adequate drugs have not yet been developed. In the past, manufacturers had been reluctant to produce such drugs: the complex process of research and marketing a drug for only a small group of potential users may bring little or no profit. This law allowed manufacturers tax benefits for portions of their research and development costs. Furthermore, if a company developed an orphan drug, it was granted exclusive marketing rights for seven years.

Drug Price Competition and Patent Term Restoration Act (1984): This law made generics, often sold at lower prices than brand-name drugs, more easily available. It also allowed drug manufacturers to "restore" part of the time spent researching drugs before approval to the patent life of the drug.

Revision of Regulations for New Drug Application Regulations (1985): Changes in requirements for manufacturers called for better organized applications, clearer data, more information on adverse reactions, quicker problem-solving, and in some instances provided for approval based on foreign studies.

Treatment Use of Investigational Drugs (1987): New regulations allowed "expanded access" protocols for promising investigational drugs. In less-restricted studies, researchers could learn more about the drug while also providing treatment for people with no effective alternative. These regulations still required researchers to formally investigate the drugs in well-controlled studies and provide reasonable evidence of effectiveness.

Accelerated Approval (1987): Before this rule, drugs could be judged only according to their effect on the illness or patients' length of survival. This regulation allowed the FDA to approve drugs based on a reasonable "surrogate endpoint"—that is, an effect of the drug on some physiological process associated with the disease (An example would be CD4 cell counts, which measure the strength of the immune system.). The "surrogate" is used to predict whether a new drug will offer therapeutic benefit. The regulation offered a way of making an apparently promising drug available without having to wait until the end of the clinical trials process. Under these rules, the FDA approves the drug only on the condition that the sponsor confirm actual clinical benefit through well-controlled studies.

Procedures for Subpart E Drugs (1988): These procedures were designed to encourage early cooperation among manufacturers, clinical researchers, and the FDA to get new drugs to patients with life-threatening or severely debilitating illnesses as quickly as possible. For example, manufacturers may request to meet with the FDA early in the drug development process to reach agreement on the design of preclinical and clinical studies. Similar meetings may also be called after phase 1 testing to discuss how to design phase 2 clinical trials, with the goal that

the data from phase 2 trials will provide sufficient data on the drug's safety and effectiveness for a decision about approval of the drug.

Parallel Track Mechanism (1992): This U.S. Public Health Service policy made promising investigational drugs for AIDS and other HIV-related diseases more widely available under "parallel track" protocols at the same time that controlled clinical trials continue. The system is designed to make the drugs available to patients who have no therapeutic alternatives and cannot participate in the controlled clinical trials. ("Controlled" studies are discussed in the section New Drugs and Clinical Trials)

Generic Drug Enforcement Act (1992): This law imposed disbarment and criminal convictions for fraudulent and illegal activities in new drug applications for generic drugs.

Prescription Drug User Fee Act (1992): Manufacturers were now required to pay fees for certain new drug applications. The funds generated have been used to add review staff at the FDA to accelerate new drug reviews. Review times for new drug applications were set at 12 months for standard applications and at 6 months for priority applications; in other words, the FDA had to take action on the application within that time frame. The order in which applications are looked at is determined with the aid of a classification system, which gives priority to drugs with the greatest potential benefit. For example, all AIDS drugs receive the highest priority, and all drugs that offer a significant medical advance over existing therapies for any disease are considered "priority drugs." The breast cancer drug Herceptin, approved in September 1998, was assigned to priority review.

Food and Drug Administration Modernization Act (1997): This extends the User Fee Act another 5 years and lowers the review times for standard new drug applications to 10 months.

From Lab to Patient Care: The Drug Approval Process

By law, the Food and Drug Administration (FDA) must review all test results for new drugs to ensure that products are safe and effective for specific uses. "Safe" does not mean that the drug is free of possible adverse side effects; rather, it means that the potential benefits have been determined to outweigh any risks. The testing process begins long before the first person takes the drug, with preliminary research and animal testing.

If a drug proves promising in the lab, the drug company or sponsor must apply for FDA approval to test it in clinical trials involving people. For drugs, the application, called an Investigational New Drug (IND) Application, is sent through the Center for Drug Evaluation and Research's (CDER) IND Review Process (http://www.fda.gov/cder/handbook/ind.htm) for biological agents, the IND is sent to the Center for Biologics Evaluation and Research (CBER) (http://www.fda.gov/cber/ind/ind.htm). Once the IND is approved by CDER or CBER, clinical trials can begin.

If the drug makes it through the clinical trials process—that is, the studies show that it is superior to current drugs—the manufacturer must submit a New Drug Application (NDA) or (for biological agents) a Biologics License Application (BLA) to the FDA. (Biological agents, such as serums, vaccines, and cloned proteins, are manufactured from substances taken from living humans or animals.) This application must include:

- The exact chemical makeup of the drug or biologic and the mechanisms by which it is effective
- Results of animal studies
- Results of clinical trials
- How the drug or biologic is manufactured, processed, and packaged
- Quality control standards
- Samples of the product in the form(s) in which it is to be administered.

Once the FDA receives the NDA or BLA from the manufacturer or developer, the formal New Drug Application Review Process (http://www.fda.gov/cder/handbook/nda.htm) or Biologics/Product License Application Review Process begins.

For an overview of the entire process from start to finish, see the CDER's visual

representation of The New Drug Development Process: Steps from Test Tube to New Drug Application Review (http://www.fda.gov/cder/handbook/develop.htm).

Speed versus Safety in the Approval Process

The FDA's current goal is that no more than ten months will pass between the time that a complete application is submitted and the FDA takes action on it. But the process is not always smooth. Sometimes FDA's external advisory call for additional research or data. In other cases, the FDA staff asks for more information or revised studies. Some new drug approvals have taken as little as 42 days; other more difficult NDAs have spent years in the approval process.

Setting Priorities

The order in which NDAs are assessed by the FDA is determined by a classification system designed to give priority to drugs with the greatest potential benefits. All drugs that offer significant medical advances over existing therapies for any disease are considered "priority" drugs in the approval process. NDAs for cancer treatment drugs are reviewed for this status primarily by the Division of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research (CDER). For Biologic License Applications (vaccines, blood products, and medicines made from animal products), the Center for Biologics Evaluation and Research (CBER) provides additional regulation and oversight.

Expert Advice

The FDA relies on a system of independent advisory committees, made up of professionals from outside the agency, for expert advice and guidance in making sound decisions about drug approval. Each committee meets as needed to weigh available evidence and assess the safety, effectiveness, and appropriate use of products considered for approval. In addition, these committees provide advice about general criteria for evaluation and scientific issues not related to specific products. The Oncologic Drugs Advisory Committee (ODAC) meets regularly to provide expert advice on cancer-related treatments and preventive drugs.

Each committee is composed of representatives from the research science and medical fields. At least one member on every advisory committee must represent the consumer perspective.

Final Approval

As the FDA looks at all the data submitted and the results of its own review, it applies two benchmark questions to each application for drug approval:

- Do the results of well-controlled studies provide substantial evidence of effectiveness?

- Do the results show the product is safe under the conditions of use in the proposed labeling? In this context, "safe" means that potential benefits have been determined to outweigh any risks.

Continued Vigilance

The FDA's responsibility for new drug treatments does not stop with final approval. The Office of Compliance in the Center for Drug Evaluation and Research (CDER) implements and tracks programs to make sure manufacturers comply with current standards and practice regulations. CDER's Office of Drug Marketing, Advertising, and Communication monitors new drug advertising to make sure it is truthful and complete. At the Center for Biologic Evaluation and Research, biologics are followed with the same vigilance after approval. And through a system called MedWatch (http://www.fda.gov/medwatch/index.html), the FDA gets feedback from health professionals and consumers on how the new drugs are working, any adverse reactions, and potential problems in labeling and dosage.

New Drugs, New Drug Uses, and Clinical Trials

Clinical trials provide the most important information used by the FDA in determining whether a new drug shows "substantial evidence of effectiveness," or whether an already-approved drug can be used effectively in new ways (for example, to treat or prevent other types of cancer, or at a different dosage). The FDA must certify that a drug has shown promise in laboratory and animal trials before human testing can begin. The trials process includes three main stages and involves continuous review, which ensures that the sponsor can stop the study early if major problems develop or unexpected levels of treatment benefit are found. As with all clinical trials, benefits and risks must be carefully weighed by the researchers conducting the study and the patients who decide to participate.

Trials for Treatment and Prevention

Clinical trials can focus on treatment (the use of a drug to treat, cure, or relieve the symptoms of a disease or condition) or prevention (the use of a drug to decrease the person's risk of developing a disease or condition). For many years, trials of cancer-related drugs focused only on treatment. This meant that almost all "cancer trials" involved people who had been diagnosed with some form of cancer.

Today, some cancer trials focus on prevention. Prevention trials include groups of people who are judged to be at increased risk for developing specific types of cancer, either because it has occurred in relatives or due to other factors such as age or lifestyle. A number of drugs, some of them used previously to treat cancer patients, are being investigated in clinical trials to determine their potential effectiveness in prevention. (Using drugs in this way is called "chemoprevention.") Drug treatment trials and chemoprevention trials have different types of participants and different emphases, but they both seek to evaluate effectiveness and safety of new drugs.

Each phase of any clinical trial for a new drug, or a new use of an existing drug, asks certain crucial questions.

- **Phase 1:** How Does the Drug Affect the Human Body? What Dosage Is Safe?
- **Phase 2:** Does the Drug Do What It's Supposed to Do?
- **Phase 3:** Is the New Drug (or New Drug Use) a Better Alternative to Current Practice?

Phase 1: How Does the Drug Affect the Human Body? What Dosage Is Safe?

In Phase 1 trials, a small number (usually between 15-30) of volunteer patients are given the drug in gradually increasing doses to assess any immediate adverse effects and to determine a safe dosage and schedule to be used in additional studies. Laboratory studies during this period also yield initial data when the drug is metabolized, or processed, inside the body—about how it is changed, which organ systems it affects, how long it stays in the body, and how the body gets rid of it. About 70% of drugs submitted for Phase 1 trials are tested successfully and go on to Phase 2 (http://www.fda.gov/fdac/special/newdrug/testtabl.html).

Often, new drugs intended to provide relief of symptoms for non-serious illnesses, such as allergy medications, can be studied in healthy volunteers because similar drugs are known to be reasonably safe. Drugs designed to treat patients with cancer, however, cannot be evaluated in this way. Many chemotherapy drugs that destroy cancer are toxic to normal cells also; this means they can cause serious side effects. Studies in animals are used to help anticipate the likelihood of particular side effects in people, but animal studies do not always predict accurately. Researchers have to weigh these risks against possible benefits very carefully before starting the trial, but there is no way to ensure that the drugs are safe at this point. Often, cancer patients who decide to participate in Phase 1 are no longer benefitting from the standard drugs that are available, or they have a type of cancer for which there is no effective treatment.

People may benefit from the treatment or chemoprevention drugs they are given in a Phase 1 trial. However, the main goal at this early stage is to see how the drug affects the body and determine appropriate dosage levels for Phase 2 studies.

Phase 2: Does the Drug Do What It's Supposed to Do?

Phase 2 trials assess the effectiveness of a new drug, or a new way of using an already-approved drug, against cancer. (For example, the drug gemcitabine, which was initially approved as a treatment for pancreatic cancer, was later evaluated in lung cancer patients and is now approved for certain types of lung cancer.) In addition, by recording adverse side effects and other data, researchers gather information on the short-term safety of the drug. In this phase, patients with specific cancer types or risk factors are given the medication to see whether or not it has a beneficial effect. Each Phase 2 study usually focuses on 30-50 patients (http://www.fda.gov/fdac/special/newdrug/testtabl.html) to determine the effects of a drug on a single type of cancer. Phase 2 bridges the information gap between "Is the drug safe?" to "Will it actually work in a specific situation?" Only about 33% of the drugs assessed in Phase 2 trials are found safe and effective enough to go on to Phase 3 (http://www.fda.gov/fdac/special/newdrug/testtabl.html).

Although information is available from Phase 1 studies, people enrolling in Phase 2 trials still may experience unexpected reactions and side effects. Beneficial effects, when they occur, may be mixed with adverse reactions. But Phase 2 trials also provide important information used in deciding whether or not a drug can proceed to Phase 3.

Phase 3: Is the New Drug (or New Drug Use) a Better Alternative to Current Practice?

By the time a new drug (or a new approach to using an approved drug) reaches Phase 3, it has shown its anti-cancer effectiveness and a safe dosage has been established. Now researchers need to figure out whether it is superior to the drugs currently used to treat a particular type of cancer or improve its symptoms, such as pain. "Superior" can mean that the drug has a more powerful anti-cancer effect, or that it is equally effective but produces fewer or less severe side effects than current drugs. In the case of a prevention trial, researchers want to know if giving the drug decreases the risk of getting cancer.

To achieve these goals, Phase 3 trials typically enroll several hundred, or even thousands, of participants drawn from cancer centers, doctor's offices, hospitals, and clinics across the nation. They also define certain criteria that people must meet before they can enter, which often have to do with the stage of the cancer (i.e., how far it has advanced), previous treatments received, and other health conditions. Through a process called **randomization**, each participant is randomly assigned (usually by computer) to one of two or more groups that will be compared throughout the trial. Scientifically, this is preferable to having doctors, researchers, or even patients decide which persons get which treatments, since random assignment makes sure every group is as similar to every other group as possible. This way of assigning treatment is ethically acceptable because physicians do not know whether the new drug really represents an advance over standard drugs.

In both treatment and prevention trials, one of the groups receives the new drug (or the new way of using an already available drug), while the other group(s) does not so they can provide a basis for comparison.

- In **treatment trials**, the other group or groups may receive: (a) a different drug already known to be effective in the disease; (b) a different dose of the drug being studied; or (c) in rare cases, no treatment at all. It's important to realize that the great majority of treatment trials in cancer are designed so that everyone receives at least the standard treatment—that is, what is currently accepted

as the best treatment. However, for certain kinds of cancer, if there really is no effective treatment, a clinical trial might be designed with a group that would receive no active treatment other than supportive care.

- In **prevention trials**, the other group or groups would receive: (a) a different drug already known to be effective; (b) a placebo or nothing at all, if no standard prevention drug exists for that condition.

The groups that do not receive the drug under investigation are called **control groups**. That is why clinical trials are sometimes described as **controlled studies**.

You may find it helpful to read through these frequently asked questions about Phase 3 drug trials.

Does this mean I might enter a trial and receive no treatment at all?

As already discussed, it is very rare for a treatment trial to be designed with a control group that receives no treatment at all. This might happen only in cases of cancer where there is no effective treatment available. In the vast majority of cases, all participants receive at least the standard treatment.

Prevention trials are different because they enroll healthy individuals with an identified risk factor or factors for developing a specific type of cancer, to test whether or not a drug shows promise in lowering its incidence. Thus, since few drugs have yet been shown to reduce the risk of cancer, Phase 3 prevention trials typically include a group that does not receive the drug under investigation and one that does. However, once the prevention trial shows that the new drug has a significant effect in preventing the development of cancer, the sponsor will stop the study to make sure that all participants can receive the new drug.

How will I know the risks and benefits before I enter the trial?

Before you can can enter a Phase 1, 2, or 3 trial, you must go through a process called informed consent (http://cancertrials.nci.nih.gov/NCI_CANCER_TRIALS/zones/TrialInfo/Deciding/InformedConsent/). During this process, you would be fully informed about the trial through both a written document and an oral discussion, which review what the trial is meant to test, how long it should last, what procedures will be performed, if randomization is involved, and what is known about the possible risks and benefits. So you would know exactly how the trial is designed and what your chances are of being assigned to any one group. Those who decide to enroll in a study are willing to accept certain risks (some of which may not even be known) to help evaluate a potentially beneficial new treatment or prevention agent. Some people are not comfortable with this and decide not to enroll. Participation is an individual decision, but in all cases it should be an informed decision.

Let's say I'm in group A in a Phase 3 study and all the patients in group B begin to show marked improvement. What happens to me?

All results are carefully monitored during the trial by a Data Safety and Monitoring Committee, whose members are not connected to the trial in any other way. If early results indicate a clear advantage for one of the groups, the sponsor of the study may choose to end the trial early and establish a protocol allowing wider use of the drug before final approval for marketing. If a drug is shown to have a strongly negative effect, the trial is stopped as soon as this is known.

This is true for both treatment and prevention trials. Recently, a trial of the the drug tamoxifen (tamoxifen citrate) showed that the drug dramatically reduced the short-term risk of breast cancer. The Data Safety and Monitoring Committee and the researchers assessed the data and halted the study so that the results could be made widely available and all women in the study could have the opportunity to take the drug. Researchers submitted a new application to FDA, which granted priority review status and was the basis for FDA approval of tamoxifen for this indication.

After the trial is over, can I find out which group I was in?

At the completion of a trial (which may sometimes include follow-up data collection), all patients have access to the results of the study and to information about their own participation. In many cases, however, this information is not available right away. Participants sometimes need to wait for data to be compiled, for other participants to finish their parts of the trial, and for investigators to analyze the results.

How do I find out about participation in clinical trials?

You should consult first with your attending physician about whether participation in such a study is appropriate for you. He or she may already know of a study or be able to direct you to a nearby resource. Another section of this Web site (http://cancertrials.nci.nih.gov/NCI_CANCER_TRIALS/zones/TrialInfo/Finding/) offers links to a number of resources for finding specific clinical trials. For example, NCI's PDQ database is a searchable online resource that includes information and contact names and phone numbers for clinical trials being conducted nationwide. Many NCI-designated Cancer Centers across the country also offer access to clinical trials. Links to these and other resources, as well as helpful hints about searching for trials, are featured in that section of the cancerTrials site.

Special Needs: Getting Drugs to Patients Who Need Them

Not everyone is eligible to participate in a clinical trial. Some patients do not fit the exact requirements for studies, some have rare forms of cancer for which only a limited number of studies are underway, and others are too ill to participate. Working with the NCI and other sponsors, the FDA has established special conditions under which a patient and his or her physician can apply to receive cancer drugs that have not yet been through the approval process. In the past, these special case applications for new drugs were grouped under the name "compassionate uses." More recently, such uses have expanded to include more patients and more categories of investigational drugs.

"Group C" Drugs

In the 1970s, researchers from the NCI became concerned about the lag between the date when an investigational drug was found to have anti-tumor activity and the time that drug became available on the market. Working with the FDA, the NCI established the "Group C" classification to allow access to drugs with reproducible activity. Group C drugs are provided to properly trained physicians who have registered using a special form to assure that their patient qualifies under guideline protocols for the drug. Each Group C drug protocol specifies patient eligibility, reporting methodology, and drug use. Not only does Group C designation (now called Group C/Treatment INDs) speed new drugs to patients who need them most, but the process also allows the NCI to gather important information on the safety as well as activity of the drugs in the settings in which they will be most used after final FDA approval. Drugs are placed in the Group C category by agreement between the FDA and the NCI. Group C drugs are always provided free of charge, and the Health Care Financing Administration provides coverage for care associated with Group C therapy.

Treatment INDs

In 1987, the FDA began authorizing the use of new drugs still in the development process to treat certain seriously ill patients. In these cases, the process is referred to as a treatment investigational new drug application (Treatment IND). Clinical trials of the new drug must already be underway and have demonstrated positive results that are reproducible. The FDA sets guidelines about what constitutes serious and life-threatening illnesses, how much must already be known about a drug's side effects and benefits, and where physicians can obtain the drug for treatment. For many seriously ill patients, the risks associated with taking a not-yet-completely proven drug are outweighed by the possible benefits.

Accelerated Approval

"Accelerated approval" is the short-hand term for the FDA's new review system which, in the 1990s, has been used to ensure rapid approval while at the same time putting new safeguards into place. Accelerated approval is based on "surrogate endpoint" judgments: FDA can grant marketing approval to drugs and treatments that, according to certain indicators, prove they are likely to have beneficial effects on a disease or condition, even before such direct benefits have been shown clinically. Accelerated approval does NOT mean that additional clinical trials are not needed or that FDA stops gathering information about the effects of the drug; a follow-up study is required to demonstrate activity by more conventional endpoints.

Snapshots: Cancer Treatments and the FDA Approval Process

These snapshots offer a look at the ways in which some recent approvals have added to the availability of cancer treatments:

Pain Relief for Patients with Prostate Cancer

Novantrone (mitoxantrone; Immunex Corporation):new use approved November 1996; initially approved in 1988 for treatment of acute nonlymphocytic leukemia.

Prostate cancer is the second leading cause of cancer deaths in the United States, with more than 300,000 new cases diagnosed each year. Of these, more than 40,000 annually will become resistant to hormone therapy. Many of these patients experience intense pain as cancer cells multiply and spread to the bone.

Mitoxantrone has been approved since 1988 for treatment of acute nonlymphocytic leukemia. The application for its use in combination with steroids to treat pain from prostate cancer was granted a priority review status. Within the year, mitoxantrone was approved for treatment of acute pain in prostate cancer. Mitoxantrone does not affect survival, but provides a palliative (pain-relieving) treatment.

Hope for Patients with Cancers of the Pancreas and Lung

Gemzar (gemcitabine; Eli Lilly and Co.): approved May 1996 for pancreatic cancer; later approved for lung cancer in 1998.

Pancreatic cancer affects more than 27,000 people in the United States each year and is the fourth leading cause of cancer deaths. The approval of Gemzar in May 1996 for the treatment of locally advanced or metastatic pancreatic cancer marked the first new treatment for the disease in several decades.

After two studies showed promise, both in tumor shrinkage and one-year survival rates, the FDA allowed access to Gemzar through a Treatment IND in 1995. More than 2,500 patients received the drug as a Treatment IND before final approval in August 1996. Clear benefits in clinical trials and the Treatment IND were shown.

In 1998, it was approved for use in combination with the chemotherapy drug cisplatin to treat patients with inoperable, locally advanced or metastatic non-small cell lung cancer.

When Established Drugs Find New Applications

Nolvadex (tamoxifen citrate; Zeneca Pharmaceutical, Inc.): new use approved October 1998.

Tamoxifen has been used as an effective breast cancer treatment for more than 20 years. As part of cancer prevention trials conducted by NCI's National Surgical Adjuvant Breast and Bowel Project (NSABP), tamoxifen was the focus of a controlled clinical trial with women judged to be at high risk for developing breast cancer. The trial was halted 14 months early, in March 1998, when interim results showed that tamoxifen reduced breast cancer incidence or risk by almost one-half.

Preventing cancer with new drug therapies involves identifying potentially effective therapies and those groups of patients at risk for developing specific cancers. The application of clinical trials to cancer prevention promises to provide the basis for many beneficial drug approvals in the next decade.

Selected Cancer Drugs Approved by the FDA in 1998 and 1999

Since 1998, 25 new drugs and new uses for already-approved drugs have been approved by the FDA to help cancer patients. Below are a few examples:

- *Ontak (denileukin diftitox; Ligand Pharmaceuticals)*: received accelerated approval (based on tumor reduction) on February 5, 1999 for the treatment of certain cases of persistent or recurrent cutaneous t-cell lymphoma, (CTCL), a rare slow-growing form of non-Hogkin's lymphoma (applicability determined by certain characteristics of the malignant cells).

- *Zofran ODT (odansetron; Glaxo Wellcome, Inc)*: received additional approval on January 27, 1999 for prevention of chemotherapy and radiation-induced nausea and vomiting, and prevention of postoperative nausea and vomiting (new dosage form).

- *Actiq (fentanyl citrate; Anesta Corporation)*: received approval on November 4, 1998 for management of chronic pain in cancer patients that are experiencing breakthrough pain on their regular narcotic (opioid) therapy.

- *Camptosar (irinotecan hydrochlorise; Pharmacia & Upjohn)*: received additional approval on October 22, 1998 for the treatment of patients with metastatic colon or rectal cancer whose disease has recurred or progressed following chemotherapy.

- *Zoladex (goserelin acetate implant; Zeneca Pharmaceuticals)*: received additional approval on July 27, 1998 for use of certain dosages in combination with flutamide for the management of locally confined prostate cancer.

- *Taxol (paclitaxel; Bristol-Myers Squibb Pharmaceutical Research Institute)*: received additional approval on June 30, 1998 for use in combination with the chemotherapy drug cisplatin, for the treatment of non-small cell lung cancer in patients who are not candidates for surgery or radiation.

- *Xeloda (capecitabine; Hoffman-La Roche)*: received accelerated approval on April 30, 1998 for treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen, or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated.

For the complete list, see the FDA's Drug Approvals for Cancer Indications (http://www.fda.gov/oashi/cancer/cdrug.html).

Online Resources for Understanding the Drug Approval Process and the Role of Clinical Trials

A note on the use of Internet resources.

Through the Internet, patients today have access to almost limitless references and resources on cancer care and treatment. By logging on, a patient may find a support group of people with the same disease, learn of new and promising treatments, or read in depth about the medical implications of existing therapies.

But not all cancer information on the Internet is sound. Offers of cancer "cures" and miraculous drugs are at best misleading and may be fraudulent. Great care should be exercised in determining which sites carry sound advice backed by legitimate medical research. If you find something that sounds promising, ask your doctor for professional advice before requesting more information or taking any action. For more information, see our **10 Things to Know about Evaluating Medical Resources on the Web** (http://trialdev.nci.nih.gov/NCI_CANCER_TRIALS/zones/TrialInfo/Resources/surf.html).

The following information from the FDA should help you better understand the drug approval process:

Center for Drug Evaluation and Research
(http://www.fda.gov/cder/handbook)

"**From Test Tube to Patient: New Drug Development in the U.S**".—a special January 1995 issue of the magazine FDA Consumer
(http://www.fda.gov/special/newdrug/ndd_toc.html)

Milestones in U.S. Food and Drug Law History
(http://www.fda.gov/opacom/backgrounders/miles.html)

Drug Approvals for Cancer Indications
(http://www.fda.gov/oashi/cancer/cdrug.html).

Explanation of Terms

Accelerated Approval— A mechanism intended to speed approval of drugs promising significant benefit over existing therapy for serious or life-threatening illnesses. It incorporates elements aimed at making sure that rapid approval is balanced by safeguards to protect both the public health and the integrity of the regulatory process. This mechanism may be used when approval can be reliably based on evidence of a drug's effect on a surrogate endpoint (see below), or when FDA determines an effective drug can be used safely only under restricted distribution or use. Usually, such a surrogate can be assessed much sooner than such an endpoint as survival. In accelerated approval, FDA approves the drug on condition that the sponsor study the actual clinical benefit of the drug.

Advisory Committee— A panel of outside experts convened periodically to advise FDA on safety and efficacy issues about drugs and other FDA-regulated products. FDA isn't bound to take committee recommendations, but usually does.

Biologic License Application (BLA)— An application requesting FDA approval to market a new biologic agent (vaccines, blood products, and medicines made from animal products) for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for FDA reviewæincluding chemistry, pharmacology, medical, biopharmaceutics, statistics, and, for anti-infectives, microbiology.

Clinical Studies— Human studies designed to distinguish a drug's effect from other influences, such as a spontaneous change in disease progression or in the effect of a placebo (an inactive substance that looks like the test drug). Such studies conducted in this country must be under an approved Investigational New Drug Application (see below), under the guidance of an institutional review board and in accord with FDA rules on human studies and informed consent of participants.

Drug Product— The finished dosage form (tablet, capsule, etc.) that contains a drug substanceægenerally, but not necessarily, in association with other active or inactive ingredients.

Drug Substance— The active ingredient intended to diagnose, treat, cure, or prevent disease or affect the structure or function of the body, excluding other inactive substances used in the drug product.

Effectiveness— The desired measure of a drug's influence on a disease condition. Effectiveness must be proven by substantial evidence consisting of adequate and

well-controlled investigations, including human studies by qualified experts, that prove the drug will have the effect claimed in its labeling.

Investigational New Drug Application (IND)— An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

New Drug— A drug first investigated or proposed for marketing after 1938 (when the Federal Food, Drug, and Cosmetic Act was passed)æthat is, the drug was not generally recognized as safe and effective before that date.

New Drug Application (NDA)— An application requesting FDA approval to market a new drug for human use in interstate commerce. The application must contain, among other things, data from specific technical viewpoints for FDA reviewæincluding chemistry, pharmacology, medical, biopharmaceutics, statistics, and, for anti-infectives, microbiology.

Parallel Track Mechanism— A U.S. Public Health Service policy that makes promising investigational drugs for AIDS and other HIV-related diseases more widely available under parallel track protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. This system is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

Pharmacology— The science that deals with the effect of drugs on living organisms.

Preclinical Studies— Studies that test a drug on animals and other nonhuman test systems. They must comply with FDA's good laboratory practices. Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies). Also, because animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on offspring.

Safety— No drug is completely safe or without the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of results of tests adequate to show the drug is safe under the conditions of use in the proposed labeling. Thus, safety is determined case by case and reflects the drug's risk-vs.-benefit relationship.

Supplement— A marketing application submitted for changes in a product that already has an approved NDA. FDA must approve all important NDA changes (in packaging or ingredients, for instance) to ensure that the conditions originally set for the product are not adversely affected.

Surrogate Endpoint— A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. An example would be CD4 cell counts, used to measure the strength of the immune system.

Toxicity— Specific degree to which a substance is harmful or poisonous.

Treatment IND— A mechanism that allows promising investigational drugs to be used in expanded access protocolsærelatively unrestricted studies in which the intent is both to learn more about the drugs, especially their safety, and to provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative. But these expanded access protocols also require researchers to formally investigate the drugs in well-controlled studies and to supply some evidence that the drugs are likely to be helpful. The drugs cannot expose patients to unreasonable risk.

User Fees— Charges to drug firms for certain NDAs, drug products, and manufacturing establishments. FDA uses these fees to hire more application reviewers and to accelerate reviews through the use of computer technology.